Higher Systolic Blood Pressure Is Associated With Increased Water Diffusivity in Normal-Appearing White Matter

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Background and Purpose—Hypertension is associated with the development of white matter lesions in older people. Diffusion tensor MRI can detect subtle, previsible white matter damage, but relationships between diffusion tensor MRI parameters and blood pressure (BP) remain unclear. We examined correlations among mean diffusivity (MD), fractional anisotropy and BP in 45 men aged 71 to 76 years.

Methods—MD and fractional anisotropy were measured in 6 regions of interest in normal-appearing white matter. Visible white matter lesions were quantified using the Fazekas scale. Both were correlated with systolic and diastolic BP.

Results—Systolic BP was positively and significantly correlated with MD in all 6 regions ($r=0.31$ to $0.45$; $P=0.037$ to 0.002). MD was also correlated with diastolic BP in the genu of the corpus callosum ($r=0.34$, $P=0.018$). A summary factor derived from principal component analysis of the MD measurements accounted for 53.8% of the variance and correlated at $r=0.51$ ($P<0.001$) with systolic BP and $r=0.33$ ($P=0.028$) with diastolic BP. Fractional anisotropy did not correlate significantly with BP. Deep white matter Fazekas scores correlated with diastolic BP ($p=0.35$, $P=0.019$).

Conclusions—the increase in MD without change in fractional anisotropy indicates that, in normal-appearing white matter, higher BP may be associated with increased extracellular fluid before any cytoarchitectural damage occurs. (Stroke. 2009;40:00-00.)

Key Words: blood pressure ▪ brain imaging ▪ diffusion tensor imaging ▪ MRI ▪ white matter

Vascular risk factors such as hypertension, diabetes, hyperlipidemia, and smoking have all been linked with an increased risk of developing white matter lesions (WMLs). However, the relationship between more subtle, previsible white matter (WM) damage as detected by diffusion tensor MRI (DT-MRI) and hypertension is unclear. Nitkunan and coworkers examined large regions of interest (ROIs) in centrum semiovale that included both normal and abnormal-appearing WM and reported that compared with controls, patients with hypertension had significantly higher fractional anisotropy (FA) but not mean diffusivity (MD). Huang and coworkers compared FA values (MD not reported) in hypertensive patients versus controls in several ROIs placed in normal-appearing WM, but found significant differences only in occipital WM. No published studies have yet examined the relationships between DT-MRI measures of WM integrity and blood pressure (BP) across normotensive and hypertensive ranges in the same population. We examined the relationship between BP and DT-MRI measures of WM integrity in normal-appearing WM in 45 men aged 71 to 76 years. We hypothesized that higher BP would be associated with reduced WM integrity, that is, increased MD and reduced FA.

Materials and Methods

Participants

Subjects were 45 community-dwelling male volunteers aged from 71 to 76 (mean, 73.2 years; SD, 1.3) without history of stroke, cancer, depression, or dementia and recruited through an invitation letter and medical interview. All subjects underwent cognitive screening and had Mini-Mental State Examination scores between 24 and 30. The Lothian Research Ethics Committee approved the study and all subjects gave informed consent.

Magnetic Resonance Imaging

MRI data were collected on a GE Sigma 1.5T (Milwaukee, Wisc) scanner. Participants received axial T2-weighted and fluid-attenuated inversion recovery sequences (field of view 220×220 mm, matrix 256×256, 24 contiguous slices of 5.6-mm thickness). The DT-MRI protocol used single-shot spin-echo echoplanar imaging and consisted of 3 T2-weighted and sets of diffusion-weighted ($b=1000$ s/mm$^2$) axial volumes acquired with diffusion gradients applied in 51 noncolinear directions. Forty-eight contiguous slice locations were imaged (field of view 220×220 mm, matrix 128×128, slice thickness 2.8 mm) coincident with the volume covered by the T2- and fluid-attenuated inversion-weighted scans.
Image Analysis
Bulk patient motion and eddy current-induced artifacts were removed from the DT-MRI data using FSL (FMRIB, Oxford, UK; www.fmrib.ox.ac.uk), and MD and FA volumes were generated for every subject.

Using the coregistered $T_2$-weighted echoplanar imaging volumes and with reference to the $T_2$- and fluid-attenuated inversion recovery-weighted volumes, 4 small square ROIs (9 voxels, volume 74.4 mm$^3$) were placed bilaterally in normal-appearing frontal, occipital, parietal, and temporal WM and one ROI in the center of the genu and splenium of corpus callosum. Two ROIs (4 voxels, 33.1 mm$^3$) were also placed bilaterally in the genu and splenium (Figure). These regions were sampled in every slice in which they were clearly visible, typically 3 to 5 slices, giving an average of between 64 and 100 ROIs per subject. To minimize gray matter and cerebrospinal fluid signal contamination, ROIs were placed centrally in each WM region avoiding WMLs and at least one voxel away from the edge of the ventricles. Mean values of MD and FA were calculated from the average of the left and right hemisphere values plus the central ROI in the case of the genu and splenium of corpus callosum for each of these regions in every subject.

WMLs in deep (DWML) and periventricular (PVWML) WM were assessed by a neuroradiologist using the Fazekas scale.$^4$ This widely used scale rates DWML and PVWML separately using a 4-point scale for each with WMLs scored from 0 (absent) to 3 (marked abnormality).

Blood Pressure Measurements
Systolic and diastolic BP values were the mean of 3 readings taken after the participants had been sitting for 5 minutes in a quiet room.

Statistical Analysis
Pearson correlations were used to test the hypothesis that increased MD and decreased FA were associated with higher systolic and diastolic BP. MD and FA data from the 6 regions were subjected to principal component analysis to derive summary factors for MD and FA. These factors represent the shared variance among the regional measurements of MD and FA. We examined correlations between WML load and BP using Spearman's $\rho$. Probability values <0.05 were considered significant.

Results
The mean of Mini-Mental State Examination scores was 27.9 (SD, 1.9). Of the 45 subjects, 10 (22%) were on treatment for hypertension and 2 (4%) had diabetes. The mean systolic BP was 148.6 (SD, 19.5) and mean diastolic BP was 81.9 (9.4) mm Hg. Mean body mass index was 26.6 kg/m$^2$ (SD, 3.0).

The numbers of participants in each category of the Fazekas DWML scale were 14 for Category 0, 24 for Category 1, 5 for Category 2, and 2 for Category 3. Likewise for the PVWML scale, 8 were in Category 0, 28 in Category 1, 5 in Category 2, and 4 in Category 3. Thus, most participants had either none or few WMLs. There were no significant correlations between Fazekas scores and systolic BP. DWML Fazekas scores correlated significantly and positively with diastolic BP ($r=0.35$, $P=0.019$), and there was a trend for a correlation between PVWML scores and diastolic BP ($r=0.29$, $P=0.059$).

Tables 1 and 2 show descriptive statistics for MD and FA and correlations between MD and BP. MD was positively and significantly correlated with systolic BP in all 6 regions ($r=0.31$ to 0.45; $P=0.007$ to 0.002) and with diastolic BP in the genu of corpus callosum ($r=0.34$, $P=0.018$). Principal component analysis yielded an MD summary factor accounting for 53.8% of the variance among the MD measurements and an FA summary factor accounting for 40.7% of the variance among the FA measurements. The MD summary factor correlated at $r=0.51$ ($P<0.001$) with systolic BP and $r=0.33$ ($P=0.028$) with diastolic BP. Neither FA nor the FA summary factor was significantly associated with systolic or diastolic BP in any region. Controlling for age, body mass index, and smoking, or excluding the 2 participants with diabetes, did not affect the overall pattern of results.

To investigate whether these correlations might be due to partial volume averaging of normal-appearing WM and WMLs, subjects with Fazekas scores of 2 or 3 in either or both the DWML and PVWML scales were excluded from the analysis. Repeating this analysis with the remaining 33 subjects did not affect the overall pattern of results with correlations between MD and systolic BP remaining statistically significant for the MD summary factor and 4 of the 6 regions (Supplemental Table I; available at http://stroke.ahajournals.org).

Discussion
The main novel finding of this study was that higher systolic BP was associated with higher MD in all 6 WM regions.
studied. Relationships between diastolic BP and MD were less strong, although they were significant in one region and showed trends in the predicted direction in 4 of the 5 remaining regions. FA did not correlate with BP in any region. Diastolic BP was associated with increased numbers of visible WMLs in deep WM.

These findings are consistent with the hypothesis that BP elevation across a range of “normal” and hypertensive values is associated with increasing degrees of WM damage in both normal-appearing WM and with the number of visible WMLs. However, only MD showed significant correlations with BP in normal-appearing WM. How should this be interpreted? Visible WMLs are associated with increased BP, but there is considerable debate as to how these abnormalities are formed and to the mechanisms linking hypertension with WM damage. Although WMLs are considered to be ischemic in origin, and blood flow may be reduced in established WMLs, it is not known how WMLs are initiated. MD is thought predominantly to reflect the amount of mobile water in the extracellular space, whereas FA reflects intact cellular cytoarchitecture, in particular fiber coherence and integrity. It could be that more tissue damage is required to cause a significant change in FA than in MD. The increased extracellular water, as measured by MD, could be explained if hypertension, even modest BP elevation, were associated with pathological increases in blood–brain barrier permeability leading to more accumulation of fluid in the extracellular space before sufficient cell damage has occurred to reduce the microstructural integrity of the WM as measured by FA or produce a visible lesion. Such a thesis would support the view that alterations in blood–brain barrier permeability are a significant early part of the etiology of WM pathology. Indeed, we have recently shown that increased permeability is associated with the phenotype of cerebral small vessel disease.

Values of MD and FA presented here are similar to those reported in other studies of aging. For example, using a similar ROI methodology as used here, O’Sullivan et al measured MD and FA values for frontal, parietal, and occipital white matter of 809 (39), 750 (36) and 829 (40) × 10−6 mm2/s and 0.34 (0.04), 0.31 (0.02), and 0.38 (0.03), respectively, in 17 healthy subjects aged 71.8 (7.9) years.

Some limitations of this preliminary study are that the results apply only to men, the sample size was relatively small, BP was measured on only one occasion although the mean of 3 readings was used, and some participants were taking antihypertensive medication. (Performing a subgroup analysis on the 35 subjects not taking antihypertensive medication did not significantly alter the pattern of correlations described here.) However, the consistent pattern of results suggests that the sample size was sufficient to indicate genuine associations between BP and MD in this sample. Another potential limitation is that multiple correlations were used leading to the risk of Type I statistical error. However, our hypotheses were clearly prespecified, and the significant correlations between the MD summary factor (accounting for the majority of the variance in the MD measurements) and both systolic and diastolic BP suggest that these results reflect genuine relationships in this sample.

In summary, these findings suggest that variations in BP across the normotensive and hypertensive range may be associated with subvisible WM damage in older people. Larger longitudinal studies are now required to confirm this observation and explore further the sequence of events leading to visible WM damage. DT-MRI measures may also provide a valuable method of monitoring any early neuroprotective effects of antihypertensive drugs.

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### Disclosures
None.

### References
### Table I. Correlations Between MD and BP for the 6 WM Regions Investigated in Participants With Fazekas Scores of 0 or 1 in Both DWML and PVWML Scales (N=33)*

<table>
<thead>
<tr>
<th></th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD summary factor†</td>
<td>0.50 (P=0.003)</td>
<td>0.30 (P=0.09)</td>
</tr>
<tr>
<td>Frontal</td>
<td>0.41 (P=0.007)</td>
<td>0.27 (P&gt;0.10)</td>
</tr>
<tr>
<td>Temporal</td>
<td>0.53 (P=0.002)</td>
<td>0.34 (P=0.053)</td>
</tr>
<tr>
<td>Parietal</td>
<td>0.35 (P=0.045)</td>
<td>0.17 (P&gt;0.10)</td>
</tr>
<tr>
<td>Occipital</td>
<td>0.30 (P=0.085)</td>
<td>0.07 (P&gt;0.10)</td>
</tr>
<tr>
<td>Genu</td>
<td>0.39 (P=0.025)</td>
<td>0.24 (P&gt;0.10)</td>
</tr>
<tr>
<td>Splenium</td>
<td>0.26 (P&gt;0.10)</td>
<td>0.23 (P&gt;0.10)</td>
</tr>
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*Bold type indicates correlations significant at the P<0.05 level.
†First component of a principal component analysis of the MD measurements in the 6 regions investigated in the original 45 subjects. This component accounted for 53.8% of the shared variance among these regions.
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